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Causes of death in children with congenital anomalies up to age 10 in 8 European countries

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Causes of death in children with congenital anomalies up to age 10 in 8 European countries

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Abbreviations:

95% CI	95% Confidence Interval;
CA	Congenital Anomaly
CHD	Congenital Heart Defect
EUROCAT	Establishing a linked European Cohort of Children with Congenital Anomalies
ICD-9	International Statistical Classification of Diseases and Related Health Problems, Ninth Revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ONS	Office for National Statistics
UK	United Kingdom

Article Summary
Through linkage of congenital anomaly (CA) registries with mortality records, this study analyses the causes of death in children under 10 years with major CA

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Joachim Tan, Anke Rissmann, Svetlana V. Glinianaia, Judith Rankin, Maria Loane, Joan K. Morris, Ester Garne
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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abstract

Background

Congenital anomalies (CAs) increase the risk of death during infancy and childhood. This study aimed to evaluate the accuracy of using death certificates to estimate the burden of CAs on mortality for children under 10 years old.

Methods

Children born alive with a major CA between 1st January 1995 and 31st December 2014, from 13 population-based European CA registries were linked to mortality records up to their 10th birthday or 31st December 2015, whichever was earlier.

Results

In total 4,199 neonatal, 2,100 post-neonatal and 1,087 deaths in children aged 1 to 9 years were reported. The underlying cause of death was a CA in 71% (95% CI: 64%-78%) of neonatal and 68% (95% CI: 61%-74%) of post-neonatal infant deaths. For neonatal deaths the proportions varied by registry from 45% to 89% and by anomaly from 53% for Down syndrome to 94% for Tetralogy of Fallot. In children aged 1-9, 49% (95% CI: 42%-57%) were attributed to a CA. Comparing mortality in children with anomalies to population mortality predicts that over 90% of all deaths at all ages are attributable to the anomalies. The exact ICD9/ICD10 CA code was often not reported for any cause of death, even for lethal anomalies such as Trisomy 13 (20% with incorrect codes).

Conclusions

Data on the underlying cause of death from death certificates alone are not sufficient to evaluate the burden of CAs on infant and childhood mortality across countries and over time. Linked data from CA registries and death certificates are necessary for obtaining accurate estimates.

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Background

The contribution of congenital anomalies (CAs) to causes of early death is increasing as mortality from other causes declines globally.[1] The Global Burden of Disease study estimated that, worldwide in 2010, CAs accounted for 6.4% of neonatal deaths, 2.2% of post-neonatal and 2.5% of deaths in children under 5 years of age.[2] In comparison, in Europe from 2000-2015, CAs were estimated to account for 26% of all deaths in infants, 16% in children aged 1-4 and 9% in children aged 5-9.[3]

The above estimates of the burden of disease in populations have all been derived from data on the underlying cause of death recorded on death certificates. Such data is often used to monitor any changes in primary and secondary prevention over time[1, 4, 5] and for international comparisons.[6, 7] However, the accuracy of cause of death on death certificates has often been questioned, and a US study concluded that linking CA registries to death certificates was necessary to provide a comprehensive picture of the full burden of CAs on mortality in infants and children.[8] This EUROlinkCAT study linked live births with a major CA reported to 13 EUROCAT (European network for the epidemiological surveillance of CAs) registries[9] to national/regional databases on vital statistics/mortality up to their 10th birthday. The aim was to determine what the children with CAs died from and whether their CA was mentioned anywhere on the death certificate. This information should improve interpretation of mortality rates routinely reported for children with CAs in Europe.

Method

Thirteen population-based EUROCAT CA registries from eight countries linked their data on live born children with a major CA, born between 1st January 1995 and 31st December 2014, to mortality records up to the child's 10th birthday or to 31st December 2015, whichever was earlier (Table 1). Ten registries linked to vital statistics containing civil registrations data (e.g.

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births, deaths and emigrations) but three were able to link to death registrations only. Both deterministic and probabilistic linkage methods were used. Linkage rates were high, with 8 registries linking over 95% of cases and only one registry linking less than 90% of the births. Additional details evaluating the linkage are provided elsewhere.[10, 11]

Classification of Anomalies

The EUROCAT Guide 1.4 specifies the coding of all major CAs into specific CA subgroups using ICD-10 or ICD-9 - BPA (British Pediatric Association extension).[12] A child is defined as having an isolated CA if (s)he has a CA in one organ system only or as part of a known sequence (e.g. renal agenesis with pulmonary hypoplasia). A EUROCAT computer algorithm was used for classification of major CAs into isolated anomalies, multiple anomalies or genetic anomalies without a manual clinical review of the identified potential multiple CAs.[13] The severe congenital heart defect (CHD) subgroup includes types of CHD's selected due to their high mortality.[14] Forty-six CA subgroups were analysed, including anomalies likely to be recorded as an underlying cause of death (such as Trisomy 13 or 18) and anomalies less likely to be recorded on a death certificate (such as limb reduction defects or hypospadias).

Classification of cause of death

All causes of death were recorded using ICD-10 or ICD-9. Four registries were able to provide only the underlying cause of death. Other registries were able to report in addition to the underlying cause of death the primary/immediate cause of death, contributing cause of death and any other causes of death.

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Deaths were categorised into neonatal (0-27 days), post-neonatal (28-364 days) and child (365-3651 days). In England and Wales the underlying cause for neonatal deaths was not specified and each cause was classified as related to infant, mother or either[15]; main causes were listed before other (secondary) causes. For this study, in Wales, the first cause of death related to the infant was taken to be the underlying cause of death. In England, the first mention of a CA (if present) was taken to be the underlying cause.

Seven categories of cause of neonatal and post-neonatal deaths, based on a modified version of the UK Office for National Statistics' (ONS) classification of neonatal and post-neonatal causes of death[15] were used in this study (see appendix A). The 'All other conditions' group was very heterogeneous. It included neoplasms, metabolic disorders, jaundice and endocrine disorders, and external causes.

Similarly, the classification of cause of death for children aged 1 to 9 in this study was based on the UK ONS classification of causes of death[15] and was divided into 13 categories (see appendix B)

To determine the accuracy of the CA recorded on death certificates, two paediatricians agreed a set of ICD-10 and ICD-9 codes corresponding to an "exact match" for the child's anomaly and a larger set of codes that were considered as an "acceptable match" (see Appendix C). For example, for a child with spina bifida (ICD-10 code-Q05), if Q05 was on the death certificate this was considered an exact code; if there were codes for other neural tube defects Q00 (anencephaly) or Q01 (encephalocele) they were considered as acceptable codes. All the available causes of death were searched to determine if any exact or acceptable anomaly codes had been specified.

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Statistical Analysis

The analysis variables from each of the 13 registries were mapped and recoded to a common data model (full details are given in Morris et al[10]) and analysed locally using common Stata syntax scripts. Aggregate data from each registry were submitted to a Central Results Repository based at Ulster University, UK using a secure portal where they were merged and uploaded to the study team for analysis.

The predicted proportions of deaths in children with a CA attributable to that anomaly was estimated from the population mortality rate (published by WHO) for children in the 8 countries and the observed mortality rate for children with the specific CA (from an earlier EUROlinkCAT study[16]) as equal to (CA mortality - population mortality)/CA mortality. For example, if the mortality rate in children with anomalies is 10 times greater than that in the population, then for every 10 deaths in a group of children with anomalies you would expect only 1 death in a similar group of children without anomalies. Therefore it could be said that the excess 9 deaths (10-1) were attributable to the anomaly, or 90% when expressed as a proportion of all deaths in children with anomalies (9/10). These were underestimates as the population mortality included children with CAs.

To estimate the overall proportion of each cause of death specified as the underlying cause of death, multilevel multinomial models were fitted with registry as a random effect. The models were fitted in Stata using the generalised structural equation model estimation command (gsem) for each CA separately. The observed information matrix was used to obtain the variance-covariance matrix of the estimates as it is the default method. The same models were

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used to estimate the overall proportion of death certificates with the exact and appropriate CA codes. For the group of all anomalies, the proportion of all neonatal deaths with CA as an underlying cause of death was compared across the different registries in a figure to illustrate the variation between registries, with the exact method used to estimate the 95% confidence intervals.

Ethical approval

All EUROCAT registries obtained ethical, governance and other permissions for the data linkage according to their national legislations and arrangements. University of Ulster obtained Ethics permission for the Central Results Repository on 15.09.2017 (Institute of Nursing and Health Research Ethics Filter Committee, number FCNUR-17- 000)

Results

The 13 registries varied considerably in size due to the differences in populations covered and years of data available, from 1,770 deaths in Finland to only 148 in Tuscany (Table 1). The majority of deaths reported (57%) occurred in the neonatal period. Overall, 71% (95% CI: 64%-78%) of neonates who died had a CA coded as the underlying cause of death. However, this varied significantly according to registry from 89% in Malta to 45% in Tuscany (Italy) and 46% in Wales (UK) (Figure 1). Registries providing only one cause of death had a lower proportion specifying a CA as the underlying cause of death. All registries, except for Wales, had under 7% or deaths attributed to immaturity. Wales had 15% of such deaths, which together with the low proportion of CAs, may be due to the Welsh coding of infant death certificates (see methods).

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Table 1: Number of deaths and percentage by age at death in children with a major congenital anomaly reported by participating EUROCAT registries and databases

Participating registries	Included birth years	No. of livebirths	% of all live births linked	Only underlying cause of death provided	No. of deaths	Percentage of deaths (%)		
						Infants < 28 days	Infants 28-364 days	Children 1 to 9 years
Denmark, Funen*	1995-2014	2425	100.0		150	58	30	11
Finland	1995-2014	42921	99.9		1770	61	24	15
Italy, Emilia Romagna	2008-2014	5589	91.4		204	52	39	9
Italy, Tuscany	2005-2014	4312	87.2	Yes	148	48	36	16
Malta	1995-2014	2718	91#		241	69	20	11
Northern Netherlands*	1995-2014	8605	96.7	Yes	620	66	21	13
Norway	1999-2014	27201	100.0		1034	58	27	15
Spain, Basque Country	1995-2014	5904	94#	Yes	411	52	37	11
Spain, Valencian Region	2007-2014	7389	95#	Yes	416	58	30	13
United Kingdom, Thames Valley*	2005-2013	3988	96.5		295	56	30	14
United Kingdom, EMSY*	2003-2012	11587	97.3		910	52	32	16
United Kingdom, Wessex*	2004-2014	4729	91.7		330	51	33	15
United Kingdom, Wales*	1998-2014	18188	99.7		845	50	32	18
Total					7386	57	28	15

EMSY, East Midlands and South Yorkshire; EUROCAT, European Surveillance of Congenital Anomalies

* Numbers of deaths rounded to nearest multiple of 5 due to disclosure requirements

Estimated proportion as linkage was to mortality records only and completeness could not be directly estimated

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Figure 2 shows that the percentage of deaths with the underlying cause of death coded as a CA was slightly lower in the post-neonatal period, 68% (95% CI: 61%-74%), and decreased to 49% (95% CI: 42%-57%) for children who died between the ages of 1 and 9. Variations by registry for the post-neonatal period and for children aged 1 to 9 were similar to those in figure 1 in the neonatal period (see supplementary appendix).

Table 2 provides the underlying cause of death for children with specific CAs. Deaths in neonates with severe CAs were likely to have the CA coded; for example, over 90% of deaths in neonates with Trisomy 13, 18 or gastroschisis had an anomaly as the cause of death. Over 90% of births with cleft lip with or without cleft palate who died had CA as the cause of death, reflecting that these children were likely also to have had more severe anomalies, such as trisomy 13 or trisomy 18. For neonates with Down syndrome, 53% had an anomaly specified and 10% of deaths were due to immaturity. The pattern was similar for all infant deaths. For children aged 1-9, other causes of death were more prominent: for several anomalies, over 10% of deaths were due to infections. For children with Down syndrome 17% of deaths were due to neoplasms. Table 2 also shows the predicted proportion of deaths attributable to the anomalies as estimated by comparing the mortality in these children to the population mortality. These proportions were above 90% for all anomalies apart from for neonatal deaths in VSD, cleft lip with or without cleft palate and Down syndrome, and post-neonatal deaths in cleft lip with or without cleft palate and multicystic renal dysplasia.

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Table 2: Percentages of children with congenital anomalies with 95% CI according to underlying cause of death by age at death [Anomalies with <10 deaths occurring are not included]

Anomaly	Number Deaths (100%)	Congenital Anomaly	Percentage Cause of Death (95%CI) Infections	Immaturity	Other	Missing cause of death	Predicted proportion attributable to the CA
Neonatal deaths							
All Anomalies	4199	71(64-78)	1(1-2)	7(6-9)	11(8-14)	9(7-12)	93
Spina Bifida (isolated cases with or without hydrocephalus)	19	79(39-95)	0(0-0)	11(3-22)	5(1-19)	5(1-19)	97
Hydrocephalus	138	64(43-80)	1(0-4)	7(4-12)	14(8-20)	14(8-20)	97
Congenital heart defects (CHD)	1937	79(71-86)	1(1-2)	3(2-5)	9(7-13)	7(5-9)	94
Severe CHD	1254	86(78-91)	0(0-1)	2(1-3)	6(4-9)	7(4-10)	98
Transposition of great vessels (as only severe CHD)	106	91(66-98)	1(0-5)	2(0-7)	4(1-12)	3(1-10)	97
VSD (without severe CHD)	291	75(58-86)	2(1-5)	5(3-9)	13(8-19)	5(3-9)	89
ASD (without severe CHD)	153	68(45-84)	4(1-8)	9(4-15)	14(7-22)	6(3-12)	90
AVSD	153	85(65-94)	0(0-0)	5(2-11)	6(2-14)	5(2-11)	97
Tetralogy of Fallot	63	94(78-98)	0(0-0)	0(0-0)	5(2-13)	2(0-10)	94
Coarctation of aorta	188	87(75-93)	0(0-0)	2(1-5)	7(4-12)	4(2-8)	96
Cleft lip with or without cleft palate	128	91(71-98)	0(0-0)	4(1-13)	2(1-8)	2(0-7)	89
Cleft palate	121	68(46-83)	1(0-5)	12(6-18)	11(6-17)	9(5-15)	92
Oesophageal atresia	110	82(64-92)	0(0-0)	5(2-10)	6(3-12)	7(3-14)	97

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Diaphragmatic hernia (isolated cases)	186	89(76-96)	0(0-0)	2(1-5)	2(1-6)	6(3-13)	99
Gastroschisis (isolated cases)	25	92(61-99)	4(1-20)	0(0-0)	0(0-0)	4(1-20)	94
Multicystic renal dysplasia	92	67(42-85)	1(0-6)	9(4-15)	10(5-17)	13(6-20)	96
Down syndrome	102	53(33-72)	4(2-7)	10(6-15)	26(17-34)	7(3-11)	82
Trisomy 13	156	90(76-96)	0(0-0)	1(0-5)	2(1-6)	6(3-13)	100
Trisomy 18	330	93(80-98)	0(0-0)	1(0-4)	1(0-4)	5(2-12)	100

Anomaly	**Number deaths (100%)**	**Congenital Anomaly**	**Infections**	**Immaturity**	**Other**	**Missing cause of death**	**Predicted proportion attributable to the CA**
Post-neonatal deaths							
All Anomalies	2100	68(61-74)	5(4-6)	4(3-5)	20(16-22)	4(3-5)	94
Hydrocephalus	85	55(38-70)	7(4-11)	6(3-10)	29(22-34)	2(1-7)	98
Congenital heart defect	1329	75(68-82)	4(3-6)	3(2-4)	15(11-18)	3(2-4)	97
Severe CHD	773	87(79-93)	3(2-5)	1(0-2)	6(4-10)	3(2-6)	99
Transposition of great vessels (as only severe CHD)	27	100(100-100)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	97
VSD (without severe CHD)	289	67(55-77)	5(3-8)	5(3-8)	20(15-25)	2(1-4)	96
ASD (without severe CHD)	169	56(41-69)	2(1-5)	8(5-11)	30(23-35)	4(2-7)	96
AVSD	199	84(67-93)	4(2-7)	1(0-3)	9(5-16)	3(1-6)	99
Tetralogy of Fallot	85	98(66-100)	1(0-9)	0(0-6)	1(0-12)	0(0-6)	97
Coarctation of aorta	130	86(67-95)	5(2-11)	0(0-0)	6(2-12)	4(1-10)	98

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Cleft lip with or without cleft palate	53	66(45-80)	2(0-9)	0(0-0)	26(17-33)	6(2-12)	88
Cleft palate	76	70(49-84)	3(1-8)	3(1-8)	16(10-21)	9(5-15)	95
Oesophageal atresia	45	66(39-84)	5(1-11)	2(0-10)	18(10-24)	9(4-16)	97
Diaphragmatic hernia (isolated cases)	12	83(39-98)	8(1-30)	0(0-0)	8(1-30)	0(0-0)	97
Gastroschisis (isolated cases)	20	82(31-98)	5(1-17)	5(1-17)	5(1-17)	5(1-17)	94
Multicystic renal dysplasia	11	41(5-90)	0(0-0)	24(4-41)	36(6-54)	0(0-0)	72
Down syndrome	165	71(53-84)	6(3-10)	5(2-8)	16(9-23)	2(1-5)	96
Trisomy 13	35	94(69-99)	0(0-0)	0(0-0)	3(0-15)	3(0-15)	100
Trisomy 18	136	93(77-98)	0(0-0)	1(0-5)	1(0-6)	5(2-13)	100

Anomaly	**Number deaths 1- 9 years (100%)**	**Congenital Anomaly**	**Infections**	**Neoplasms**	**Nervous**	**Other**	**Missing cause of death**	**Predicted proportion attributable to the CA**
Child deaths (1-9 years)								
All Anomalies	1087	49(42-57)	9(8-10)	5(4-6)	9(8-11)	23(21-26)	4(3-5)	99
Hydrocephalus	66	49(25-73)	13(7-18)	7(3-11)	10(5-15)	17(10-21)	5(2-10)	100
Congenital heart defect	474	63(54-72)	8(6-10)	3(2-4)	4(3-5)	19(16-22)	3(2-5)	99
Severe CHD	258	79(67-87)	5(3-8)	1(0-3)	2(1-4)	10(7-13)	3(2-6)	100
VSD (without severe CHD)	100	48(31-66)	13(9-17)	6(3-10)	6(3-10)	24(18-27)	2(1-6)	99
ASD (without severe CHD)	81	44(28-61)	10(6-13)	7(4-11)	2(1-6)	31(25-32)	5(2-9)	99
AVSD	70	79(60-90)	6(2-12)	0(0-0)	0(0-0)	11(6-18)	4(2-10)	99
Tetralogy of Fallot	51	71(42-87)	10(5-15)	2(0-8)	2(0-8)	12(6-17)	4(1-10)	100

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Coarctation of aorta	44	70(43-87)	5(1-12)	0(0-0)	2(0-10)	14(7-20)	9(4-16)	99
Cleft lip with or without cleft palate	12	65(7-98)	17(1-46)	0(0-0)	0(0-0)	17(1-46)	0(0-0)	99
Cleft palate	41	67(34-89)	5(1-12)	0(0-0)	5(1-12)	16(7-27)	7(2-15)	91
Oesophageal atresia	23	47(10-88)	11(2-19)	0(0-0)	11(2-19)	26(7-37)	5(1-15)	99
Down syndrome	98	42(28-56)	14(10-18)	17(13-21)	0(0-0)	24(20-28)	2(1-6)	99
Trisomy 18	17	94(24-100)	6(0-76)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	99

95% CI, 95% Confidence Interval; ASD, Atrial septal defect; AVSD, Atrioventricular septal defect; CHD, Congenital heart defect; VSD, Ventricular Septal Defect.

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Figure 3 shows the results for all causes (including underlying causes) of death to determine if any exact/acceptable CA codes were recorded for deaths up to age 10 years. As expected, no CA code indicating a limb reduction defect was provided for any of the 165 deaths amongst children with these anomalies. Five severe conditions (anencephaly, gastroschisis, diaphragmatic hernia, trisomy 13 and trisomy 18) had over 75% of exact codes recorded as cause of death. For other severe CAs (particularly CHDs), few deaths were attributed to the anomaly. For example, Tetralogy of Fallot had an exact or acceptable code recorded for just 50% of deaths. There were also coding issues with several CAs, such as bilateral renal agenesis and atresia of bile ducts, resulting in over 30% of codes being "acceptable codes" rather than exact codes.

Discussion

This study found that only 70% of infants dying with a major CA had the underlying cause of death recorded as a CA, with higher percentages for those with anomalies known to be associated with high mortality, such as 86% for infants with severe CHD. Children aged 1-9 years with a major CA were less likely to have underlying cause of death recorded as a CA (49%) with other causes such as infections, trauma and cancer being more prominent[17]. By comparing the mortality rate for children with anomalies from an earlier EUROlinkCAT study[16] to published population rates it was possible to estimate that over 90% of deaths in children with anomalies are attributable to their anomaly. These results are consistent with the estimates for infant deaths in other studies, but estimates have not been reported for deaths in later childhood[8, 18, 19]. Our results show that if only the underlying cause of death on death certificates is analysed, the impact of CAs on mortality is considerably underestimated for all ages and all anomalies.

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Under-reporting is to be expected as it is not always clear if the CA is the underlying cause of death. For example a child may die from an infection and it is difficult to distinguish if the CA is the underlying cause or not as the CA does increase the risk of severe infections, making infection either more likely or more severe[20]. Similarly, many anomalies are associated with an increased risk of preterm birth. However, all registries apart from Wales, appeared to be consistent in assigning cause of death as the CA rather than the morbidity associated with being born preterm. Similar under-reporting of mortality and morbidity for children with chronic conditions has also been reported from healthcare databases.[17, 21-24]

In addition to the under-reporting on death certificates, estimating the full burden of CAs will require including data on stillbirths, miscarriages and terminations of pregnancy for CAs.[25]

Another important finding was that if a CA was mentioned on the death certificate, it may not have been the exact code. For example, for CHDs a general code indicating a heart defect was often provided rather than the code for the specific cardiac defect. Care must be taken when analysing data from death certificates if there is no method of independently verifying the coding of the anomaly. A study in the US, using information from death certificates, estimated that Trisomy 18 and CHD were the two most common causes of infant death due to CAs in term born infants, accounting for 11% and 15% of CA deaths, respectively.[6] In our study, the comparable figures using the diagnosed anomalies of the infants (not the anomalies recorded on the death certificates) are 8% for Trisomy 18 and 32% for severe CHD. Inaccuracies on death certificates are expected with the accuracy depending on the person completing the form.[26, 27] The 60% of exact codes for children with a CHD in our study is similar to the 70% recorded by a recent study from the US on deaths in infants with CHD.[28]

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The occurrence of infections and neoplasms as underlying causes of death in infants with Down syndrome reflects their known increased risk of infections and leukemia.[29]

Malta was the country most likely to record a CA as the underlying cause of death. This may be due to the fact that terminations of pregnancy for foetal anomaly is illegal in Malta and therefore more babies are born with severe life-threatening anomalies than in other countries where terminations are legal and the anomaly is likely to be detected by the prenatal screening. [30] The Nordic countries (Denmark, Finland and Norway) were more likely to record CA as the underlying cause of death compared with the other European countries. In Denmark and Finland the death certificates are completed online by using predefined ICD10 codes. Adopting this policy of standardised reporting in other countries may improve the accuracy and comparability of the data.

Strengths

The strength of this study is that it included data from 13 population-based CA registries in eight European countries. The analysis of linked cases enabled direct comparisons of the recorded anomaly codes on the death certificates with the CA diagnosis reported in the CA registries, assumed to be the gold standard. Earlier analyses of EUROlinkCAT data enabled attributable proportions to be estimated for the same CAs.

Limitations

A limitation of the study is that a child may have several anomalies and the one of interest may not be the underlying cause of death. Another limitation was the cause of death for infants was categorised into only seven categories resulting in the "All other conditions" being heterogeneous including neoplasms, metabolic disorders, jaundice and endocrine

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disorders and external causes. This unfortunately limits the interpretation of the deaths in this category. As the study was conducted by standardising the data in all registries and then providing syntax scripts to analyse it, it was not possible to redefine more meaningful categories. In addition, four registries were only able to provide one cause of death, which may not have been the underlying cause of death.

Conclusion

Data on the underlying cause of death from death certificates alone are not sufficient to evaluate the burden of CAs on infant and childhood mortality across countries and over time. Linked data from CA registries and death certificates are necessary for obtaining accurate estimates.

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What is already known on this topic:

- Infant and child mortality is a public health concern, and congenital anomalies (CAs) contribute significantly to this mortality.
- In Europe, CAs account for 26% of deaths in infants and over 10% of deaths in children aged under 10 years.
- Data on cause of death on death certificates are frequently analysed to estimate the burden of disease in populations.

What this study adds

- The recording of codes for CAs on European death certificates underestimates the proportion of deaths due to CAs by up to 30% in infants.
- Only 70% of deaths in infants with CA had a CA recorded as the underlying cause of death.
- Children aged 1-9 years with CA were less likely to have underlying cause of death recorded as a CA (49%).

How this study might affect research, practice or policy

- This information should improve interpretation of mortality rates routinely reported for children with CAs in Europe.
- Linkage of death certificates with CA registries should be used to evaluate the burden of CAs more accurately in future research.

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Figure legends:

Figure 1. For neonates with a major congenital anomaly (CA): comparison of percentage of all neonatal deaths with "Congenital Anomaly" as the underlying cause of death on the death certificate by registry

Figure 2. The distribution of causes of death in children with a major congenital anomaly (CA) according to the recorded underlying cause of death by age at death.

Figure 3. Anomaly codes on death certificates for children with a major congenital anomaly dying before their 10th birthday according to the acceptability of the ICD-9/ICD-10 code recorded (number of deaths). PDA, Patent Ductus Arteriosus, CHD, Congenital Heart Defect, GA, Gestational Age

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Causes of death in children with congenital anomalies up to age 10 in 8 European countries

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Abbreviations:

95% CI	95% Confidence Interval;
CA	Congenital Anomaly
CHD	Congenital Heart Defect
EUROCAT	Establishing a linked European Cohort of Children with Congenital Anomalies
ICD-9	International Statistical Classification of Diseases and Related Health Problems, Ninth Revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ONS	Office for National Statistics
UK	United Kingdom

Article Summary
Through linkage of congenital anomaly (CA) registries with mortality records, this study analyses the causes of death in children under 10 years with major CA

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Abstract

Background

Congenital anomalies (CAs) increase the risk of death during infancy and childhood. This study aimed to evaluate the accuracy of using death certificates to estimate the burden of CAs on mortality for children under 10 years old.

Methods

Children born alive with a major CA between 1st January 1995 and 31st December 2014, from 13 population-based European CA registries were linked to mortality records up to their 10th birthday or 31st December 2015, whichever was earlier.

Results

In total 4,199 neonatal, 2,100 post-neonatal and 1,087 deaths in children aged 1 to 9 years were reported. The underlying cause of death was a CA in 71% (95% CI: 64%-78%) of neonatal and ~~67~~68% (95% CI: 61%-~~73~~74%) of post-neonatal infant deaths. For neonatal deaths the proportions varied by registry from 45% to 89% and by anomaly from 53% for Down syndrome to 94% for Tetralogy of Fallot. In children aged 1-9, 49% (95% CI: 42%-57%) were attributed to a CA. Comparing mortality in children with anomalies to population mortality predicts that over 90% of all deaths at all ages are attributable to the anomalies. The exact ICD9/ICD10 CA code was often not reported for any cause of death, even for lethal anomalies such as Trisomy 13 (20% with incorrect codes).

Conclusions

Data on the underlying cause of death from death certificates alone are not sufficient to evaluate the burden of CAs on infant and childhood mortality across countries and over time. Linked data from CA registries and death certificates are necessary for obtaining accurate estimates.

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Background

The contribution of congenital anomalies (CAs) to causes of early death is increasing as mortality from other causes declines globally.[1] The Global Burden of Disease study estimated that, worldwide in 2010, CAs accounted for 6.4% of neonatal deaths, 2.2% of post-neonatal and 2.5% of deaths in children under 5 years of age.[2] In comparison, in Europe from 2000-2015, CAs were estimated to account for 26% of all deaths in infants, 16% in children aged 1-4 and 9% in children aged 5-9.[3]

The above estimates of the burden of disease in populations have all been derived from data on the underlying cause of death recorded on death certificates. Such data is often used to monitor any changes in primary and secondary prevention over time[1, 4, 5] and for international comparisons.[6, 7] However, the accuracy of cause of death on death certificates has often been questioned, and a US study concluded that linking CA registries to death certificates was necessary to provide a comprehensive picture of the full burden of CAs on mortality in infants and children.[8] This EUROlinkCAT study linked live births with a major CA reported to 13 EUROCAT (European network for the epidemiological surveillance of CAs) registries[9] to national/regional databases on vital statistics/mortality up to their 10th birthday. The aim was to determine what the children with CAs died from and whether their CA was mentioned anywhere on the death certificate. This information should improve interpretation of mortality rates routinely reported for children with CAs in Europe.

Method

Thirteen population-based EUROCAT CA registries from eight countries linked their data on live born children with a major CA, born between 1st January 1995 and 31st December 2014, to mortality records up to the child's 10th birthday or to 31st December 2015, whichever was earlier (Table 1). Ten registries linked to vital statistics containing civil registrations data (e.g.

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births, deaths and emigrations) but three were able to link to death registrations only. Both deterministic and probabilistic linkage methods were used. Linkage rates were high, with 8 registries linking over 95% of cases and only one registry linking less than 90% of the births. Additional details evaluating the linkage are provided elsewhere.[10, 11]

Classification of Anomalies

The EUROCAT Guide 1.4 specifies the coding of all major CAs into specific CA subgroups using ICD-10 or ICD-9 - BPA (British Pediatric Association extension).[12] A child is defined as having an isolated CA if (s)he has a CA in one organ system only or as part of a known sequence (e.g. renal agenesis with pulmonary hypoplasia). A EUROCAT computer algorithm was used for classification of major CAs into isolated anomalies, multiple anomalies or genetic anomalies without a manual clinical review of the identified potential multiple CAs.[13] The severe congenital heart defect (CHD) subgroup includes types of CHD's selected due to their high mortality.[14] Forty-six CA subgroups were analysed, including anomalies likely to be recorded as an underlying cause of death (such as Trisomy 13 or 18) and anomalies less likely to be recorded on a death certificate (such as limb reduction defects or hypospadias).

Classification of cause of death

All causes of death were recorded using ICD-10 or ICD-9. Four registries were able to provide only the underlying cause of death. Other registries were able to report in addition to the underlying cause of death the primary/immediate cause of death, contributing cause of death and any other causes of death.

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Deaths were categorised into neonatal (0-27 days), post-neonatal (28-364 days) and child (365-3651 days). In England and Wales the underlying cause for neonatal deaths was not specified and each cause was classified as related to infant, mother or either[15]; main causes were listed before other (secondary) causes. For this study, in Wales, the first cause of death related to the infant was taken to be the underlying cause of death. In England, the first mention of a CA (if present) was taken to be the underlying cause.

Seven categories of cause of neonatal and post-neonatal deaths, based on a modified version of the UK Office for National Statistics' (ONS) classification of neonatal and post-neonatal causes of death[15] were used in this study (see appendix A). The 'All other conditions' group was very heterogeneous. It included neoplasms, metabolic disorders, jaundice and endocrine disorders, and external causes.

Similarly, the classification of cause of death for children aged 1 to 9 in this study was based on the UK ONS classification of causes of death[15] and was divided into 13 categories (see appendix B)

To determine the accuracy of the CA recorded on death certificates, two paediatricians agreed a set of ICD-10 and ICD-9 codes corresponding to an "exact match" for the child's anomaly and a larger set of codes that were considered as an "acceptable match" (see Appendix C). For example, for a child with spina bifida (ICD-10 code-Q05), if Q05 was on the death certificate this was considered an exact code; if there were codes for other neural tube defects Q00 (anencephaly) or Q01 (encephalocele) they were considered as acceptable codes. All the available causes of death were searched to determine if any exact or acceptable anomaly codes had been specified.

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Statistical Analysis

The analysis variables ~~Data~~ from each of the 13 registries were ~~standardised, i.e. analysis variables were~~ mapped and recoded to a common data model (full details are given in Morris et al[10]) and analysed locally using common Stata syntax scripts. Aggregate data from each registry were submitted to a Central Results Repository based at Ulster University, UK using a secure portal where they were merged and uploaded to the study team for analysis.

~~The proportion of all neonatal deaths with CA as an underlying cause of death was compared across the different registries using a random effects meta-analysis of the proportions with the Freeman-Tukey Double Arcsine Transformation to stabilise the variances using the metaprop command in Stata version 16.~~

The predicted proportions of deaths in children with a CA attributable to that anomaly was estimated from the population mortality rate (published by WHO) for children in the 8 countries and the observed mortality rate for children with the specific CA (from an earlier EUROlinkCAT study[16]) as equal to (CA mortality - population mortality)/CA mortality. For example, if the mortality rate in children with anomalies is 10 times greater than that in the population, then for every 10 deaths in a group of children with anomalies you would expect only 1 death in a similar group of children without anomalies. Therefore it could be said that the excess 9 deaths (10-1) were attributable to the anomaly, or 90% when expressed as a proportion of all deaths in children with anomalies (9/10). These were underestimates as the population mortality included children with CAs.

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To estimate the overall proportion of each cause of death specified as the underlying cause of death, multilevel multinomial models were fitted with registry as a random effect. The models were fitted in Stata using the generalised structural equation model estimation command (gsem) for each CA separately. ~~The same models were used to estimate the overall proportion of death certificates with the exact and appropriate CA codes.~~ The observed information matrix was used to obtain the variance-covariance matrix of the estimates as it is the default method. The same models were used to estimate the overall proportion of death certificates with the exact and appropriate CA codes. For the group of all anomalies, the proportion of all neonatal deaths with CA as an underlying cause of death was compared across the different registries in a figure to illustrate the variation between registries, with the exact method used to estimate the 95% confidence intervals. ~~The same models were used to estimate the overall proportion of death certificates with the exact and appropriate CA codes.~~

Ethical approval

All EUROCAT registries obtained ethical, governance and other permissions for the data linkage according to their national legislations and arrangements. University of Ulster obtained Ethics permission for the Central Results Repository on 15.09.2017 (Institute of Nursing and Health Research Ethics Filter Committee, number FCNUR-17- 000)

Results

The 13 registries varied considerably in size due to the differences in populations covered and years of data available, from 1,770 deaths in Finland to only 148 in Tuscany (Table 1). The majority of deaths reported (57%) occurred in the neonatal period. Overall, 71% (95% CI: 64%-78%) of neonates who died had a CA coded as the underlying cause of death. However, this varied significantly according to registry from 89% in Malta to 45% in Tuscany (Italy) and

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46% in Wales (UK) (Figure 1). Registries providing only one cause of death had a lower proportion specifying a CA as the underlying cause of death. All registries, except for Wales, had under 7% or deaths attributed to immaturity. Wales had 15% of such deaths, which together with the low proportion of CAs, may be due to the Welsh coding of infant death certificates (see methods).

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Table 1: Number of deaths and percentage by age at death in children with a major congenital anomaly reported by participating EUROCAT registries and databases

Participating registries	Included birth years	No. of livebirths	% of all live births linked	Only underlying cause of death provided	No. of deaths	Percentage of deaths (%)		
						Infants < 28 days	Infants 28-364 days	Children 1 to 9 years
Denmark, Funen*	1995-2014	2425	100.0		150	58	30	11
Finland	1995-2014	42921	99.9		1770	61	24	15
Italy, Emilia Romagna	2008-2014	5589	91.4		204	52	39	9
Italy, Tuscany	2005-2014	4312	87.2	Yes	148	48	36	16
Malta	1995-2014	2718	91#		241	69	20	11
Northern Netherlands*	1995-2014	8605	96.7	Yes	620	66	21	13
Norway	1999-2014	27201	100.0		1034	58	27	15
Spain, Basque Country	1995-2014	5904	94#	Yes	411	52	37	11
Spain, Valencian Region	2007-2014	7389	95#	Yes	416	58	30	13
United Kingdom, Thames Valley*	2005-2013	3988	96.5		295	56	30	14
United Kingdom, EMSY*	2003-2012	11587	97.3		910	52	32	16
United Kingdom, Wessex*	2004-2014	4729	91.7		330	51	33	15
United Kingdom, Wales*	1998-2014	18188	99.7		845	50	32	18
Total					7386	57	28	15

EMSY, East Midlands and South Yorkshire; EUROCAT, European Surveillance of Congenital Anomalies

* Numbers of deaths rounded to nearest multiple of 5 due to disclosure requirements

Estimated proportion as linkage was to mortality records only and completeness could not be directly estimated

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Figure 2 shows that the percentage of deaths with the underlying cause of death coded as a CA was slightly lower in the post-neonatal period, 68% (95% CI: 61%-74%), and decreased to 49% (95% CI: 42%-57%) for children who died between the ages of 1 and 9. Variations by registry for the post-neonatal period and for children aged 1 to 9 were similar to those in figure 1 in the neonatal period (see supplementary appendix).

Table 2 provides the underlying cause of death for children with specific CAs. Deaths in neonates with severe CAs were likely to have the CA coded; for example, over 90% of deaths in neonates with Trisomy 13, 18 or gastroschisis had an anomaly as the cause of death. Over 90% of births with cleft lip with or without cleft palate who died had CA as the cause of death, reflecting that these children were likely also to have had more severe anomalies, such as trisomy 13 or trisomy 18. For neonates with Down syndrome, 53% had an anomaly specified and 10% of deaths were due to immaturity. The pattern was similar for all infant deaths. For children aged 1-9, other causes of death were more prominent: for several anomalies, over 10% of deaths were due to infections. For children with Down syndrome 17% of deaths were due to neoplasms. Table 2 also shows the predicted proportion of deaths attributable to the anomalies as estimated by comparing the mortality in these children to the population mortality. These proportions were above 90% for all anomalies apart from for neonatal deaths in VSD, cleft lip with or without cleft palate and Down syndrome, and post-neonatal deaths in cleft lip with or without cleft palate and ~~Multicystic~~ multicystic renal dysplasia.

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Table 2: Percentages of children with congenital anomalies with 95% CI according to underlying cause of death by age at death [Anomalies with <10 deaths occurring are not included]

Anomaly	Number Deaths (100%)	Congenital Anomaly	Percentage Cause of Death (95%CI) Infections	Immaturity	Other	Missing cause of death	Predicted proportion attributable to the CA
Neonatal deaths							
All Anomalies	4199	71(64-78)	1(1-2)	7(6-9)	11(8-14)	9(7-12)	93
Spina Bifida (isolated cases with or without hydrocephalus)	19	79(39-95)	0(0-0)	11(3-22)	5(1-19)	5(1-19)	97
Hydrocephalus	138	64(43-80)	1(0-4)	7(4-12)	14(8-20)	14(8-20)	97
Congenital heart defects (CHD)	1937	79(71-86)	1(1-2)	3(2-5)	9(7-13)	7(5-9)	94
Severe CHD	1254	86(78-91)	0(0-1)	2(1-3)	6(4-9)	7(4-10)	98
Transposition of great vessels (as only severe CHD)	106	91(66-98)	1(0-5)	2(0-7)	4(1-12)	3(1-10)	97
VSD (without severe CHD)	291	75(58-86)	2(1-5)	5(3-9)	13(8-19)	5(3-9)	89
ASD (without severe CHD)	153	68(45-84)	4(1-8)	9(4-15)	14(7-22)	6(3-12)	90
AVSD	153	85(65-94)	0(0-0)	5(2-11)	6(2-14)	5(2-11)	97
Tetralogy of Fallot	63	94(78-98)	0(0-0)	0(0-0)	5(2-13)	2(0-10)	94
Coarctation of aorta	188	87(75-93)	0(0-0)	2(1-5)	7(4-12)	4(2-8)	96
Cleft lip with or without cleft palate	128	91(71-98)	0(0-0)	4(1-13)	2(1-8)	2(0-7)	89
Cleft palate	121	68(46-83)	1(0-5)	12(6-18)	11(6-17)	9(5-15)	92
Oesophageal atresia	110	82(64-92)	0(0-0)	5(2-10)	6(3-12)	7(3-14)	97

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Diaphragmatic hernia (isolated cases)	186	89(76-96)	0(0-0)	2(1-5)	2(1-6)	6(3-13)	99
Gastroschisis (isolated cases)	25	92(61-99)	4(1-20)	0(0-0)	0(0-0)	4(1-20)	94
Multicystic renal dysplasia	92	67(42-85)	1(0-6)	9(4-15)	10(5-17)	13(6-20)	96
Down syndrome	102	53(33-72)	4(2-7)	10(6-15)	26(17-34)	7(3-11)	82
Trisomy 13	156	90(76-96)	0(0-0)	1(0-5)	2(1-6)	6(3-13)	100
Trisomy 18	330	93(80-98)	0(0-0)	1(0-4)	1(0-4)	5(2-12)	100

Anomaly	**Number deaths (100%)**	**Congenital Anomaly**	**Infections**	**Immaturity**	**Other**	**Missing cause of death**	**Predicted proportion attributable to the CA**
Post-neonatal deaths							
All Anomalies	2100	687(61-7374)	5(4-6)	4(3-5)	20(16-22)	4(3-5)	94
Hydrocephalus	85	55(38-70)	7(4-11)	6(3-10)	29(22-34)	2(1-7)	98
Congenital heart defect	1329	75(68-82)	4(3-6)	3(2-4)	15(11-18)	3(2-4)	97
Severe CHD	773	87(79-93)	3(2-5)	1(0-2)	6(4-10)	3(2-6)	99
Transposition of great vessels (as only severe CHD)	27	100(100-100)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	97
VSD (without severe CHD)	289	67(55-77)	5(3-8)	5(3-8)	20(15-25)	2(1-4)	96
ASD (without severe CHD)	169	56(41-69)	2(1-5)	8(5-11)	30(23-35)	4(2-7)	96
AVSD	199	84(67-93)	4(2-7)	1(0-3)	9(5-16)	3(1-6)	99
Tetralogy of Fallot	85	98(66-100)	1(0-9)	0(0-6)	1(0-12)	0(0-6)	97
Coarctation of aorta	130	86(67-95)	5(2-11)	0(0-0)	6(2-12)	4(1-10)	98

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Cleft lip with or without cleft palate	53	66(45-80)	2(0-9)	0(0-0)	26(17-33)	6(2-12)	88
Cleft palate	76	70(49-84)	3(1-8)	3(1-8)	16(10-21)	9(5-15)	95
Oesophageal atresia	45	66(39-84)	5(1-11)	2(0-10)	18(10-24)	9(4-16)	97
Diaphragmatic hernia (isolated cases)	12	83(39-98)	8(1-30)	0(0-0)	8(1-30)	0(0-0)	97
Gastroschisis (isolated cases)	20	82(31-98)	5(1-17)	5(1-17)	5(1-17)	5(1-17)	94
Multicystic renal dysplasia	11	41(5-90)	0(0-0)	24(4-41)	36(6-54)	0(0-0)	72
Down syndrome	165	71(53-84)	6(3-10)	5(2-8)	16(9-23)	2(1-5)	96
Trisomy 13	35	94(69-99)	0(0-0)	0(0-0)	3(0-15)	3(0-15)	100
Trisomy 18	136	93(77-98)	0(0-0)	1(0-5)	1(0-6)	5(2-13)	100

Anomaly	**Number deaths 1- 9 years (100%)**	**Congenital Anomaly**	**Infections**	**Neoplasms**	**Nervous**	**Other**	**Missing cause of death**	**Predicted proportion attributable to the CA**
Child deaths (1-9 years)								
All Anomalies	1087	49(42-57)	9(8-10)	5(4-6)	9(8-11)	23(21-26)	4(3-5)	99
Hydrocephalus	66	49(25-73)	13(7-18)	7(3-11)	10(5-15)	17(10-21)	5(2-10)	100
Congenital heart defect	474	63(54-72)	8(6-10)	3(2-4)	4(3-5)	19(16-22)	3(2-5)	99
Severe CHD	258	79(67-87)	5(3-8)	1(0-3)	2(1-4)	10(7-13)	3(2-6)	100
VSD (without severe CHD)	100	48(31-66)	13(9-17)	6(3-10)	6(3-10)	24(18-27)	2(1-6)	99
ASD (without severe CHD)	81	44(28-61)	10(6-13)	7(4-11)	2(1-6)	31(25-32)	5(2-9)	99
AVSD	70	79(60-90)	6(2-12)	0(0-0)	0(0-0)	11(6-18)	4(2-10)	99
Tetralogy of Fallot	51	71(42-87)	10(5-15)	2(0-8)	2(0-8)	12(6-17)	4(1-10)	100

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Coarctation of aorta	44	70(43-87)	5(1-12)	0(0-0)	2(0-10)	14(7-20)	9(4-16)	99
Cleft lip with or without cleft palate	12	65(7-98)	17(1-46)	0(0-0)	0(0-0)	17(1-46)	0(0-0)	99
Cleft palate	41	67(34-89)	5(1-12)	0(0-0)	5(1-12)	16(7-27)	7(2-15)	91
Oesophageal atresia	23	47(10-88)	11(2-19)	0(0-0)	11(2-19)	26(7-37)	5(1-15)	99
Down syndrome	98	42(28-56)	14(10-18)	17(13-21)	0(0-0)	24(20-28)	2(1-6)	99
Trisomy 18	17	94(24-100)	6(0-76)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	99

95% CI, 95% Confidence Interval; ASD, Atrial septal defect; AVSD, Atrioventricular septal defect; CHD, Congenital heart defect; VSD, Ventricular Septal Defect.

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Figure 3 shows the results for all causes (including underlying causes) of death to determine if any exact/acceptable CA codes were recorded for deaths up to age 10 years. As expected, no CA code indicating a limb reduction defect was provided for any of the 165 deaths amongst children with these anomalies. Five severe conditions (anencephaly, gastroschisis, diaphragmatic hernia, trisomy 13 and trisomy 18) had over 75% of exact codes recorded as cause of death. For other severe CAs (particularly CHDs), few deaths were attributed to the anomaly. For example, Tetralogy of Fallot had an exact or acceptable code recorded for just 50% of deaths. There were also coding issues with several CAs, such as bilateral renal agenesis and atresia of bile ducts, resulting in over 30% of codes being "acceptable codes" rather than exact codes.

Discussion

This study found that only 70% of infants dying with a major CA had the underlying cause of death recorded as a CA, with higher percentages for those with anomalies known to be associated with high mortality, such as 86% for infants with severe CHD. Children aged 1-9 years with a major CA were less likely to have underlying cause of death recorded as a CA (49%) with other causes such as infections, trauma and cancer being more prominent[17]. By comparing the mortality rate for children with anomalies from an earlier EUROlinkCAT study[16] to published population rates it was possible to estimate that over 90% of deaths in children with anomalies are attributable to their anomaly. These results are consistent with the estimates for infant deaths in other studies, but estimates have not been reported for deaths in later childhood[8, 18, 19]. Our results show that if only the underlying cause of death on death certificates is analysed, the impact of CAs on mortality is considerably underestimated for all ages and all anomalies.

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Under-reporting is to be expected as it is not always clear if the CA is the underlying cause of death. For example a child may die from an infection and it is difficult to distinguish if the CA is the underlying cause or not as the CA does increase the risk of severe infections, making infection either more likely or more severe[20]. Similarly, many anomalies are associated with an increased risk of preterm birth. However, all registries apart from Wales, appeared to be consistent in assigning cause of death as the CA rather than the morbidity associated with being born preterm. Similar under-reporting of mortality and morbidity for children with chronic conditions has also been reported from healthcare databases.[17, 21-24]

In addition to the under-reporting on death certificates, estimating the full burden of CAs will require including data on stillbirths, miscarriages and terminations of pregnancy for CAs.[25]

Another important finding was that if a CA was mentioned on the death certificate, it may not have been the exact code. For example, for CHDs a general code indicating a heart defect was often provided rather than the code for the specific cardiac defect. Care must be taken when analysing data from death certificates if there is no method of independently verifying the coding of the anomaly. A study in the US, using information from death certificates, estimated that Trisomy 18 and CHD were the two most common causes of infant death due to CAs in term born infants, accounting for 11% and 15% of CA deaths, respectively.[6] In our study, the comparable figures using the diagnosed anomalies of the infants (not the anomalies recorded on the death certificates) are 8% for Trisomy 18 and 32% for severe CHD. Inaccuracies on death certificates are expected with the accuracy depending on the person completing the form.[26, 27] The 60% of exact codes for children with a CHD in our study is similar to the 70% recorded by a recent study from the US on deaths in infants with CHD.[28]

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The occurrence of infections and neoplasms as underlying causes of death in infants with Down syndrome reflects their known increased risk of infections and leukemia.[29]

Malta was the country most likely to record a CA as the underlying cause of death. This may be due to the fact that terminations of pregnancy for foetal anomaly is illegal in Malta and therefore more babies are born with severe life-threatening anomalies than in other countries where terminations are legal and the anomaly is likely to be detected by the prenatal screening. [30] The Nordic countries (Denmark, Finland and Norway) were more likely to record CA as the underlying cause of death compared with the other European countries. In Denmark and Finland the death certificates are completed online by using predefined ICD10 codes. Adopting this policy of standardised reporting in other countries may improve the accuracy and comparability of the data.

Strengths

The strength of this study is that it included data from 13 population-based CA registries in eight European countries. The analysis of linked cases enabled direct comparisons of the recorded anomaly codes on the death certificates with the CA diagnosis reported in the CA registries, assumed to be the gold standard. Earlier analyses of EUROlinkCAT data enabled attributable proportions to be estimated for the same CAs.

Limitations

A limitation of the study is that a child may have several anomalies and the one of interest may not be the underlying cause of death. Another limitation was the cause of death for infants was categorised into only seven categories resulting in the "All other conditions" being heterogeneous including neoplasms, metabolic disorders, jaundice and endocrine

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disorders and external causes. This unfortunately limits the interpretation of the deaths in this category. As the study was conducted by standardising the data in all registries and then providing syntax scripts to analyse it, it was not possible to redefine more meaningful categories. In addition, four registries were only able to provide one cause of death, which may not have been the underlying cause of death.

Conclusion

Data on the underlying cause of death from death certificates alone are not sufficient to evaluate the burden of CAs on infant and childhood mortality across countries and over time. Linked data from CA registries and death certificates are necessary for obtaining accurate estimates.

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What is already known on this topic:

- Infant and child mortality is a public health concern, and congenital anomalies (CAs) contribute significantly to this mortality.
- In Europe, CAs account for 26% of deaths in infants and over 10% of deaths in children aged under 10 years.
- Data on cause of death on death certificates are frequently analysed to estimate the burden of disease in populations.

What this study adds

- The recording of codes for CAs on European death certificates underestimates the proportion of deaths due to CAs by up to 30% in infants.
- Only 70% of deaths in infants with CA had a CA recorded as the underlying cause of death.
- Children aged 1-9 years with CA were less likely to have underlying cause of death recorded as a CA (49%).

How this study might affect research, practice or policy

- This information should improve interpretation of mortality rates routinely reported for children with CAs in Europe.
- Linkage of death certificates with CA registries should be used to evaluate the burden of CAs more accurately in future research.

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Figure legends:

Figure 1. For neonates with a major congenital anomaly (CA): comparison of percentage of all neonatal deaths with "Congenital Anomaly" as the underlying cause of death on the death certificate by registry

Figure 2. The distribution of causes of death in children with a major congenital anomaly (CA) according to the recorded underlying cause of death by age at death.

Figure 3. Anomaly codes on death certificates for children with a major congenital anomaly dying before their 10th birthday according to the acceptability of the ICD-9/ICD-10 code recorded (number of deaths). PDA, Patent Ductus Arteriosus, CHD, Congenital Heart Defect, GA, Gestational Age

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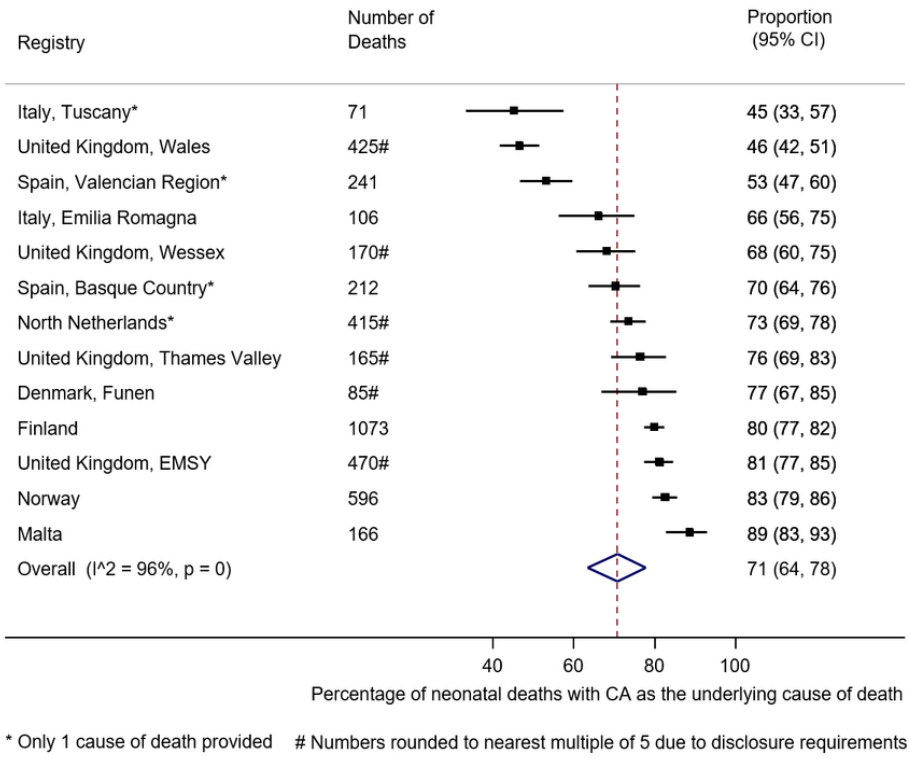

Figure 1. For neonates with a major congenital anomaly (CA): comparison of percentage of all neonatal deaths with "Congenital Anomaly" as the underlying cause of death on the death certificate by registry

39x33mm (600 x 600 DPI)

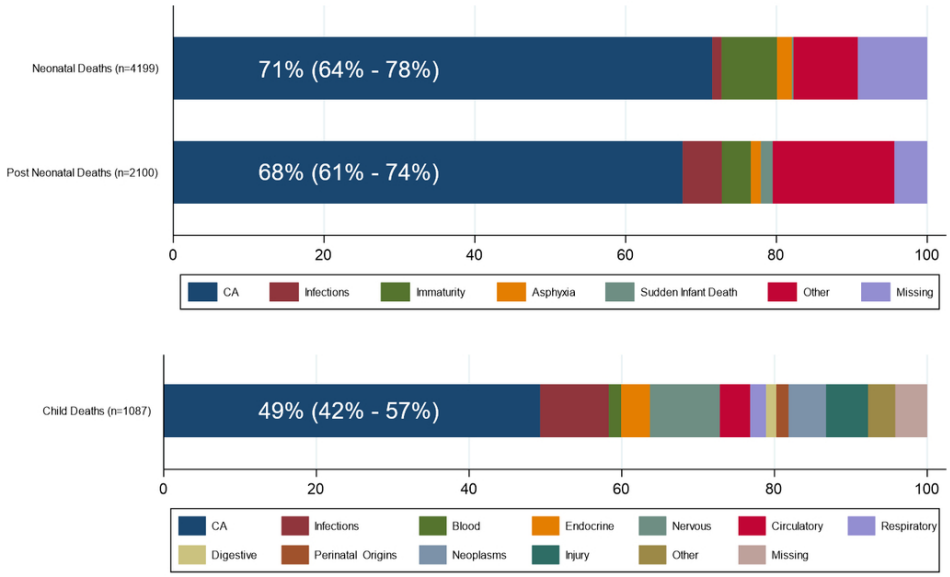

Figure 2. The distribution of causes of death in children with a major congenital anomaly (CA) according to the recorded underlying cause of death by age at death.

46x29mm (600 x 600 DPI)

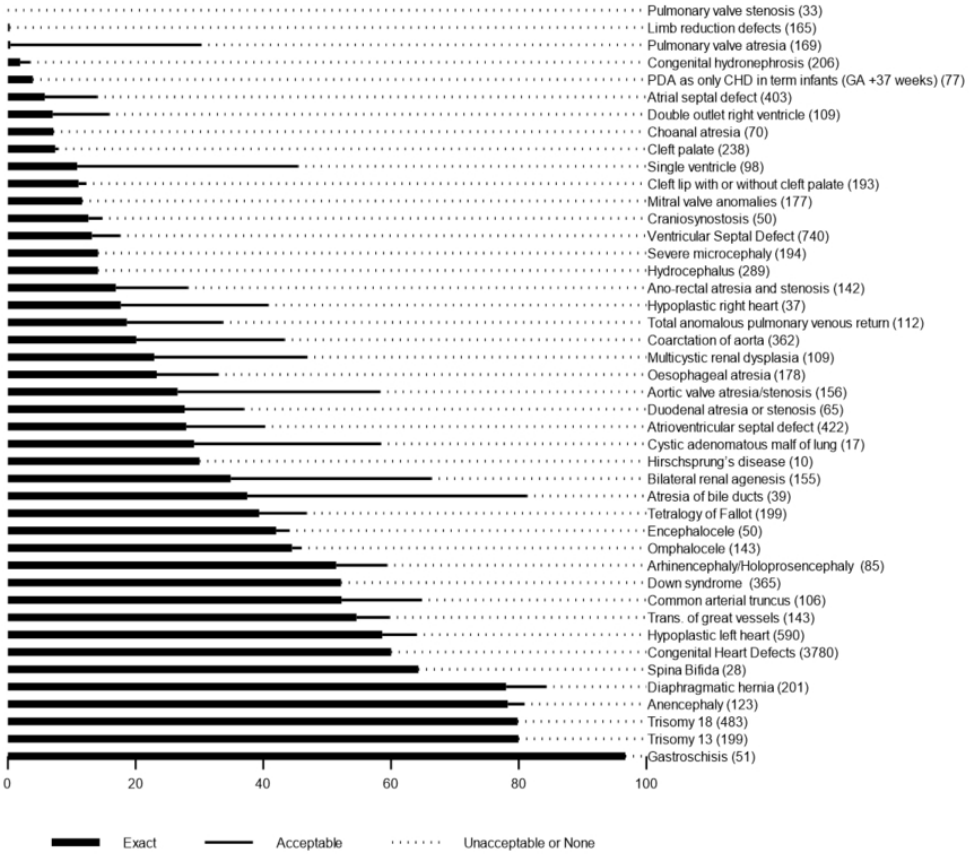

Figure 3. Anomaly codes on death certificates for children with a major congenital anomaly dying before their 10th birthday according to the acceptability of the ICD-9/ICD-10 code recorded (number of deaths). PDA, Patent Ductus Arteriosus, CHD, Congenital Heart Defect, GA, Gestational Age

37x33mm (600 x 600 DPI)

Appendix A: Classification of causes of infant death (0-364 days)

Cause of death group	ICD-10 codes	ICD-9 codes
Infections, including antepartum	A000-B99; E321, G00-G09, H650-H669, H700-H709, I300-I309, I330-I339, I400-I409, J00-J22, J36, J370-J371, J390-J391, J850-J869, K350-K359, K610-K614, K650, K659, M00-M03, N111, N12, N136, N300, N308, N390, P027, P230–P239, P350-P399 **If maternal conditions are recorded**: O353	001-134, 136-139, 254.1, 320-326, 381.0-381.4, 382.0-382.9, 383.0-383.9, 420-422, 460-465, 466, 475, 476, 478.22, 487.24, 480-488, 510, 513, 540, 566, 567.0-567.3, 567.9, 580, 590, 595.0, 595.8, 599.0, 711, 762.7, 770.0, 771.0-771.82, 771.89 No equivalent code for maternal condition.
Congenital malformations, deformations and chromosomal abnormalities	Q00-Q99	740-759
Immaturity related conditions (should be checked with gestational age at delivery)	P010–P011, P018, P070–P073, P220–P229, P250–P258†, P270–P279, P280–P289, P520–P524, P578†, P590, P77, P964	761.0-761.1, 761.8, 765.0-765.2, 769, 770.2†, 770.4-770.9, 772.1, 774.7†, 774.2, 777.5, 779.6
Asphyxia, anoxia or trauma (intrapartum)	P000, P016–P017, P020–P021, P022, P024–P026, P030–P039, P050–P059, P080–P082, P100–P159, P200–P219, P240–P241, P249, P525–P529, P90, P910–P919; **If maternal conditions are reported**: O100–O16, O363, O365, O430–O439, O440–O469, O48, O620–O689, O690–O699;	761.6-761.7, 762.0-762.1, 762.2, 762.4-762.6, 763.0-763.4, 763.6-763.9, 764.0-764.9, 766, 767.0- 767.9, 768.0-768.9, 770.10-770.14, 772.2, 779.0-779.2, 779.7 **If maternal conditions are reported**: 760.0, 762.3
Sudden infant deaths	R95-R98	798.0, 798.1-798.9

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All other conditions, including external	E40-E441, E46, J690, P242-P248, P800-P809, P810, P830-P831, P833-P839, P920-P929, V01-Y98 All other codes not listed in the groups above	260-263, 507.0; 770.15-770.18, 770-85-770.86; 778.1-778.9, 779.3, E000-E999 All other codes not listed in the groups above
Missing		

† P251, P578, 770.2 and 774.7 should be categorised under "All other conditions, including external" if gestational age at birth is ≥37 weeks.

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Appendix B: Classification of cause of death in children from 1 to 9 years of age

Cause of death group	ICD-10 codes	ICD-9 codes
I Certain Infectious and parasitic diseases plus other infectious conditions from other chapters	A00-B99, E321, G00-G09, I300-I309, I330-I339, I400-I409, J00-J22, J36, J850-J869, K350-K359, K610-K614, K650, K659, M00-MO3, N10, N111, N12, N136, N300, N308-N309, N390	001-134, 136-139, 254.1, 320-326, 420-422, 460-466, 475, 480-488, 510, 513, 540, 566, 567.0-567.3, 567.9, 580, 590, 595.0, 595.8-595.9, 599.0, 711
II Neoplasms	C00-C97; D00-D48	140-239
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89	280-289
IV Endocrine, nutritional and metabolic diseases	E00-E320, E328-E90	240-254.0, 254.8-279
VI Diseases of the nervous system	G10-G99	327-359
IX Diseases of the circulatory system	I00-I28, I310-I328, I340-I398, I41-I99	390-417, 423-459
X Diseases of the respiratory system, excluding acute infections	J300-J359, J370-J849 (excluding J690), J90-J99	470-474, 476-478, 490-496, 500-505, 511-512, 514-519
XI Diseases of the digestive system	K00-K319, K36-K605, K620-K649, K658, K660-K93	520-539, 541-543, 550-565, 567.8, 568-579
XVI Certain conditions originating in the perinatal period	P00-P96	760-779
XVII Congenital malformations, deformations and chromosomal abnormalities*	Q00-Q99*	740-759*
XIX Injury, poisoning and certain other consequences of external causes and XX External causes of morbidity and mortality	S00-S99, T00-T98, J690 (aspiration pneumonia); V01-Y89 (transport accidents – V01-V99, Other external causes of accidental injury – W00-X59 etc)	800-999 506-508; E000-E999

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All other conditions (V, VII, VIII, XII, XIII, XIV) including Undiagnosed/unclassified conditions (XVIII)	J690 (aspiration pneumonia); V01-Y89 (transport accidents – V01-V99, Other external causes of accidental injury – W00-X59 etc)	Any other codes not listed above, e.g. 290-319, 360-379, 380-389, 580-629 (excluding 580, 590, 595.0, 595.8-595.9, 599.0), 680-709, 710, 712-739; 780-799
Missing		

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Appendix C: Classification of cause of death codes concerning congenital anomalies into "exact" and "acceptable" codes, with "exact" codes taking precedence over "acceptable" codes

	ICD Codes for exact matching		ICD Codes for acceptable matching	
Group	**ICD-10**	**ICD-9**	**ICD-10**	**ICD-9**
Anencephaly	Q00	740	Q00,Q01,Q05	740 741 7420
Encephalocele	Q01	7420	Q00,Q01,Q05	740 741 7420
Spina Bifida (isolated cases with or without hydrocephalus)	Q05	741	Q00,Q01,Q05	740 741 7420
Hydrocephalus	Q03	7423	Q03	7423
Severe microcephaly	Q02	7421	Q02	7421
Arhinencephaly /holoprosencephaly	Q041, Q042	74226	Q04	742
Congenital heart defect (CHD)	Q20-Q26	745, 746, 7470-7474	Q20-Q26	745, 746, 7470-7474
Common arterial truncus	Q200	74500	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
Double outlet right ventricle	Q201	no code	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742

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Transposition of great vessels (Only severe CHD)	Q203	74510	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
Single ventricle	Q204	7453	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
Ventricular Septal Defect (without severe CHD)	Q210	7454	Q21	745
Atrial septal defect (without severe CHD)	Q211	7455	Q21	745
Atrioventricular septal defect	Q212	7456	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
Tetralogy of Fallot	Q213	7452	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232,	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742

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			Q233, Q234, Q251, Q252, Q262	
Pulmonary valve stenosis	Q221	74601	Q221	74601
Pulmonary valve atresia	Q220	74600	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
Aortic valve atresia/stenosis	Q230	7463	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
Mitral valve anomalies	Q232, Q233	7465, 7466	Q232, Q233	7465, 7466
Hypoplastic left heart	Q234	7467	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
Hypoplastic right heart	Q226	7461	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224,	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463,

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			Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	7465, 7466, 7467, 7471, 74720, 74742
Coarctation of aorta	Q251	7471	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
Total anomalous pulmonary venous return	Q262	74741 74742	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742
PDA as **only** CHD in term infants (GA +37 weeks)	Q250	7470	Q250	7470
Choanal atresia	Q300	7480	Q30	748
Cystic adenomatous malformation of lung	Q3380	74869	Q33	748
Cleft lip with or without cleft palate	Q36, Q37	7491, 7492	Q35 Q36 Q37	7490 7491 7492
Cleft palate	Q35	7490	Q35 Q36 Q37	7490 7491 7492
Oesophageal atresia with or without trachea-oesophageal fistula	Q390-Q391	75030-75031	Q38-Q45	750, 751

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Duodenal atresia or stenosis	Q410	75110	Q38-Q45	750, 751
Ano-rectal atresia and stenosis	Q420-Q423	75121-75124	Q38-Q45	750, 751
Hirschsprung's disease	Q431	75130-75133	Q38-Q45	750, 751
Atresia of bile ducts	Q442	75165	Q442, Q44	75165 or 7516
Diaphragmatic hernia	Q790	75661	Q790 or Q791	7566
Gastroschisis	Q793	75671	Q792 or Q793	75670 or 75671
Omphalocele	Q792	75670	Q792 or Q793	75670 or 75671
Bilateral renal agenesis	Q601 Q606	75300	Q60 Q61	7530 7531 7533
Multicystic renal dysplasia	Q614	75316	Q60 Q61	7530 7531 7533
Cong hydronephrosis	Q620	75320	Q62	7532
Limb reduction defects	Q71-Q73	7552-7554	Q71-Q73	7552-7554
Craniosynostosis	Q750	75600	Q75	756
VATER/VACTERL	Q8726	759895	Q8726	759895
Down syndrome	Q90	7580	Q90	7580
Trisomy 13	Q914-Q917	7581	Q914-Q917	7581
Trisomy 18	Q910-Q913	7582	Q910-Q913	7582

PDA, Patent ductus arteriosus; GA, Gestational Age.

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